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Review

Radiation and oxidative stress: A mini-review

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Abstract

Radiation, particularly ionizing radiation used in medical imaging and cancer treatments, induces oxidative stress (OS), a key factor in the biological damage it causes. Radiation interacting with biological tissues generates reactive oxygen species (ROS) that can overwhelm the cell's natural antioxidant defenses. This leads to oxidative damage to essential macromolecules such as DNA, proteins, and lipids, triggering a cascade of harmful cellular events. DNA strand breaks, protein oxidation, and lipid peroxidation are common consequences, contributing to mutations, cellular dysfunction, and apoptosis. These effects play a significant role in both acute radiation injury and long-term health outcomes, such as carcinogenesis and cardiovascular diseases. Given the growing use of radiological procedures in medicine, understanding radiation-induced OS is critical for improving patient safety. Strategies to mitigate oxidative damage, including using antioxidants and radiation dose optimization, are being actively explored. Continued research into the mechanisms of radiation-induced OS is necessary to enhance therapeutic interventions and diagnostic accuracy while minimizing potential risks. This review provides a concise summary of the relationship between radiation and OS.

Keywords

Radiology, Radiation, Oxidative Stress, Reactive Oxygen Species, Oxidative Damage

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Introduction

Wilhelm Conrad Roentgen accidentally discovered the X-rays in 1895. This discovery has created a major change not only in the field of physics but also in the field of medicine. Within months of Röntgen's discovery, X-rays were being used for medical diagnosis (1). Then, Henri Becquerel discovered radioactivity in 1896, followed by Marie and Pierre Curie's isolation of radium in 1898. Radiation falls into two categories: ionizing and non-ionizing. Non-ionizing radiation (NIR), including microwaves, infrared, ultraviolet, and visible light, can excite atoms but lacks the energy to ionize them (2,3). MRI is one of the most important medical imaging methods in which we use non-ionizing radiation. Ionizing radiation (IR) is, on the other hand, classified into electromagnetic radiation (gamma rays and X-rays) and particle radiation (electrons, protons, neutrons, and alpha particles) (4). They are possessing sufficient energy to ionize atoms. In medicine, IR is crucial for both therapy and diagnostics. It's used in nuclear medicine for treatments like radionuclide therapy and imaging techniques such as PET and in radiology for CT scans, digital subtraction angiographies (DSAs), and as well as X-ray radiography (5). Moreover, radiotherapy plays a crucial role in cancer treatment, with approximately 80% of cancer patients requiring this form of therapy (6). These advancements have fundamentally transformed how we detect and visualize diseases, as well as how we approach therapeutic intervention (5). But since the discovery of radiation, it has been a double-edged sword (7).

Biological Effects of Radiation

Scientists would gradually discover the biological effects of the radiation. By 1897, epigastric dermatitis was reported as a side effect of X-ray exposure (8). The link between radiation exposure and cancer development wasn't immediately apparent. This grim connection became evident through the tragic fates of two groundbreaking scientists in the field of radioactivity. Marie Sklodowska-Curie, a Nobel Prize recipient and trailblazer in radiation research, succumbed to aplastic anemia resulting from her prolonged radiation exposure. Similarly, her daughter, Irene Joliot-Curie, who, along with her husband, was awarded a Nobel Prize for their pioneering work on artificial radioactivity, later died from leukemia induced by radiation (9).

Within three decades after the discovery of Roentgen, a wealth of scientific literature emerged, documenting the wide-ranging effects of ionizing radiation on diverse substances and biological systems, from the visibly damaged hands of pioneering radiologists to more insidious consequences such as sterility, bone disease, cancer, and various other illnesses (10, 11). The atomic bombings of Hiroshima and Nagasaki led to extensive studies on radiation effects. Most of the information on the health risks of radiation in healthy populations comes from the life span studies, which were established after the detonation of the atomic bombs in Japan in 1945. Assembled in 1950, these cohorts have been followed for 65 years (12). It showed a direct link exists between radiation dose and solid cancer risk, with children being more vulnerable; high doses increase the risk of heart disease and other non-cancer illnesses; exposure in the womb affected brain development and raised cancer risk; interestingly, no clear increase in birth defects or illnesses was found in survivors' children; high doses impacted the immune system similarly to aging; while cancer risk increases at moderate to high doses (over 0.1-0.2 Gy), the effects of low doses (under 0.1 Gy) remain uncertain. Several large cohort studies support the life span study's findings on low-dose radiation effects. These include studies of UK nuclear workers (13), Techa River residents (14), Chornobyl cleanup workers (15), and residents of high natural radiation areas in China (16).

Effects of Oxidative Damage on Macromolecules

Oxidative damage, primarily caused by the excessive generation of reactive oxygen species (ROS), can have profound effects on various macromolecules within cells, including DNA, proteins, and lipids (17, 18). Each of these macromolecules is critical to cellular function, and their damage can lead to significant biological consequences (19). Figure 1.

DNA Damage: ROS can attack the nucleotides within DNA, leading to base modifications, strand breaks, and crosslinking (20). These mutations can interfere with DNA replication and transcription, potentially leading to errors in protein synthesis. If not properly repaired, DNA damage may result in genomic instability, which is a precursor to cancer, aging, and various genetic disorders (21).

Protein Oxidation: Proteins are vulnerable to oxidative damage, particularly in their amino acid residues. This can lead to the alteration of protein structure, loss of enzymatic activity, and impaired cellular signaling pathways (22). The accumulation of oxidized proteins is often associated with neurodegenerative diseases like Alzheimer's and Parkinson's, as well as impaired immune and metabolic functions.

Lipid Peroxidation: Lipids, especially polyunsaturated fatty acids in cell membranes, are highly susceptible to ROS attack, leading to lipid peroxidation. This process compromises the structural integrity and fluidity of cell membranes, disrupting essential functions such as ion transport, cell signaling, and energy production (23). Lipid peroxidation products can also form toxic aldehydes, further amplifying cellular damage and inflammation.

Carbohydrate Damage: Although less frequently discussed, carbohydrates can also be oxidatively damaged, particularly through reactions that generate advanced glycation end-products (AGEs). These AGEs can impair normal cellular

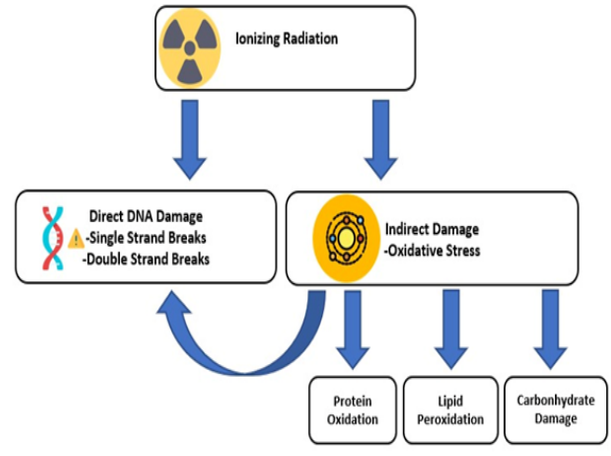

Figure 1. Effects of radiation on oxidative stress

functions by crosslinking with proteins and altering their normal activities, contributing to diabetes complications, cardiovascular diseases, and aging (24). The cumulative oxidative damage to these macromolecules can initiate a cascade of deleterious effects at the cellular level, eventually affecting tissues and organs. This contributes to a range of pathological conditions, including cancer, neurodegeneration, cardiovascular diseases, and chronic inflammation. Understanding these mechanisms underlines the importance of controlling oxidative stress through both intrinsic antioxidant defenses and potential therapeutic interventions.

DNA Damage from Ionizing Radiation: The Role of Oxidative Stress as an Indirect Pathway

The concept that ionizing radiation (IR) can harm genetic material, such as by breaking chromosomes, was recognized before we understood DNA's structure. Initially, scientists proposed a direct mechanism where high-energy particles or photons directly collided with DNA strands (25). However, later research revealed an indirect pathway involving oxidative stress (OS), which is now believed to cause most (60-70%) of IR-induced DNA damage (26-30). Oxidative stress occurs when there's an imbalance between oxidant production and antioxidant activity, favoring the former. This OS-mediated indirect mechanism involves the generation of reactive oxygen species (ROS) through IR-induced water radiolysis (4).

Ionizing radiation's impact on cells is a complex and rapid process. Within a fraction of a second after exposure, the radiation releases electrons that break chemical bonds in cellular molecules. This creates unstable particles called free radicals and ROS. Some DNA damage occurs instantly from direct radiation hits, but most happens indirectly through these newly created particles. Interestingly, the majority of DNA damage takes place within the first 5 minutes after exposure. After this initial burst, the rate of new damage slows down (4, 31). This timing is crucial for scientists studying radiation effects, as they need to measure damage quickly before cells begin their natural repair processes (32). While some ROS are neutralized, those near the cell's nucleus can be particularly harmful. They can cause severe DNA damage, especially double-strand breaks (DSBs), which are considered the most dangerous type (26-28, 30, 33-36). If not repaired correctly, these DSBs can alter chromosome structure, potentially leading to mutations. Over time, these mutations might contribute to cancer development (37-39).

Biomarkers and Assessment of the IR-Damage

Cells respond to IR-caused DNA damage by modifying a protein called H2AX, creating γ-H2AX. Scientists use this modified protein as a marker to measure the extent of DNA damage. This cellular response is part of the body's attempt to detect and repair the harm caused by radiation (40).

Radioprotective agents and Anti-oxidant Supplementation

Understanding the process from initial exposure to cellular response helps researchers develop better protective measures against radiation damage and improve treatments for radiation exposure (4). Studies have investigated a variety of antioxidant compounds for their potential to mitigate radiation-induced damage. Research has shown that certain ingredients can reduce lethality or decrease markers of DNA and cellular damage caused by radiation exposure. These include quercetin (41, 42), which has demonstrated protective effects in several studies, and astaxanthin(43), known for its potent antioxidant properties. Zeaxanthin (44), vitamin C (45), and vitamin B12 (46) have also been examined for their radioprotective potential. Additionally, selenium(47), folate (48), and CoQ10 (49, 50) have been the subject of research focusing on their ability to counteract radiation damage. Studies have also explored the benefits of α-lipoic acid and vitamin E in this context. These investigations suggest that these antioxidants might offer protection against radiation-induced cellular harm.

Conclusion Remarks

OS is an important consideration in radiology, particularly in imaging modalities that rely on ionizing radiation, such as X-rays, CT scans, and fluoroscopy. The ionization process leads to the generation of ROS, which can damage cellular components like DNA, proteins, and lipids. Although the body has natural antioxidant defenses, prolonged or excessive exposure to radiation can overwhelm these mechanisms, leading to oxidative damage and potential long-term health risks, including cancer and cardiovascular diseases. The clinical implications highlight the need for optimized protocols to minimize radiation exposure without compromising diagnostic efficacy. This includes employing the principle of ALARA (As Low As Reasonably Achievable), using advanced imaging technologies that require lower doses of radiation, and exploring protective agents that can mitigate oxidative damage. Further research is crucial to better understand the mechanisms of radiation-induced oxidative stress and to develop strategies for safeguarding patients, particularly those requiring repeated imaging. Ultimately, the balance between effective diagnostic imaging and the prevention of OS remains a key objective in the field of radiology. With ongoing advancements, radiologists and healthcare providers can continue to improve patient safety while delivering high-quality diagnostic care.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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